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The Association between Long-Term Air Pollution and Urinary Catecholamines: Evidence from the Multi-Ethnic Study of Atherosclerosis

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Background: Autonomic nervous system effects have been hypothesized as a mechanism of air pollutant health effects, though scant prior epidemiologic research has examined the association between air pollutants and catecholamines.

Objectives: To examine the association of long-term air pollutants with three urinary catecholamines: dopamine (DA), epinephrine (EPI), and norepinephrine (NE). As a secondary aim, we also examined the association between short-term (or acute) exposure to fine particulate matter [particulate matter with aerodynamic diameter $\leq 2.5 \mu m$ ($PM_{2.5}$)] and those catecholamines.

Methods: We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) and two of its ancillary studies, the MESA Air Pollution Study and the MESA Stress Study, to provide exposure and outcome data. DA, EPI, and NE from urine samples were collected from 2004 to 2006 from 1,002 participants in the New York, New York, and Los Angeles, California, study sites. Spatiotemporal models incorporated cohort-specific monitoring and estimated annual average pollutant concentrations ($PM_{2.5}$, NO_2, NO_x and black carbon) at participants' homes the year prior to urine collection. Secondarily, short-term $PM_{2.5}$ was evaluated (day of, day prior, and 2- to 5-d lags prior to urine collection). Several covariates were considered confounders (age, race, sex, site, socioeconomic status, cardiovascular disease risk factors, psychosocial stressors, and medication use) in linear regression models.

Results: A 17 ppb higher annual NO_x concentration was associated with 6.3% higher mean EPI level [95% confidence interval (CI): 0.3%, 12.6%]. A 2-$\mu g/m^3$ higher annual ambient $PM_{2.5}$ concentration was associated with 9.1% higher mean EPI (95% CI: 3.2%, 15.3%) and 4.4% higher DA level (95% CI: 1%, 7.9%). NO_2, black carbon, and short-term $PM_{2.5}$ exposures were not significantly associated with any of the catecholamines.

Conclusions: We found an association between EPI and long-term concentrations of $PM_{2.5}$ and NO_x and an association between DA and long-term ambient $PM_{2.5}$. These novel findings provide modest support for the hypothesis that air pollutant exposures are related to sympathetic nervous system activation. https://doi.org/10.1289/EHP3286

Introduction

Catecholamines act as both neurotransmitters and hormones produced by the sympathetic branch of the autonomic nervous system (ANS). Among other things, catecholamines play an important role in regulating heart rate and blood pressure, and elevated catecholamine levels have been implicated in heart failure (Floras 2003). One hypothesized mechanism by which air pollution results in acute cardiovascular health effects is through increased activation of the sympathetic nervous system (SNS). Animal, epidemiologic, and controlled exposure studies have examined the effect of a variety of short-term pollutants on heart rate and heart rate variability, markers of cardiac autonomic control (Brook and Rajagopalan 2010; Cosselman et al. 2015). Fewer human studies, however, have directly studied the response of catecholamines to inhaled pollution (Li et al. 2017; Liu et al. 2017; Orgacka et al. 1983). Existing studies have used very different approaches (randomized experiment vs. cross-sectional observational study) and have yielded different conclusions.

Although the impacts of long-term exposures to air pollution on SNS functions have been infrequently studied, plausible biological mechanisms linking long-term exposure to air pollution to systemic levels of catecholamines have been identified. One plausible biological mechanism involves alteration of stress hormone receptors, particularly beta-adrenergic receptors. Recent work suggests that stress hormone receptors may be involved in pollutant-induced pulmonary inflammation and its downstream systemic effects; alterations of these receptors as a result of air pollution exposure may thus produce chronic health effects (Chiarella et al. 2014; Henriquez et al. 2018).

Investigating the relationship between air pollution exposures and catecholamines can therefore shed light on the mechanisms linking air pollution to chronic diseases affected by sympathetic functions, including respiratory and cardiovascular outcomes. In addition, catecholamines, specifically dopamine (DA) and norepinephrine (NE), are implicated in long-term neurodegenerative diseases such as Parkinson's and Alzheimer's; thus, this research could inform the growing literature about air pollution's effects on brain health (Block et al. 2012; Power et al. 2016). Understanding whether and how air pollution affects catecholamines may also provide a better understanding of the mechanistic underpinning of the potential joint effect of air pollution and psychosocial stress (i.e., the synergistic impact of chemical and nonchemical stressors).

The primary objective of this study was to provide epidemiologic evidence of the association between long-term air pollutants and three urinary catecholamines: epinephrine (EPI), NE, and DA. As a secondary aim, we also examined the association between short-term (or acute) exposure to fine particulate matter

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[particulate matter with aerodynamic diameter $\leq 2.5 \mu m$ ($PM_{2.5}$)], measured days prior to urine collection, and the catecholamines.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study designed to examine the progression of subclinical and clinical cardiovascular disease (CVD) among adults 45 to 84 years old and free from CVD at baseline. The study recruited 6,814 participants of black, white, Hispanic, and Chinese race/ethnicities from six U.S. study sites (Baltimore, Maryland; Chicago, Illinois; Winston-Salem, North Carolina; Los Angeles, California; New York, New York, and St. Paul, Minnesota) (Bild et al. 2002). The baseline examination was held from July 2000 to August 2002, with four follow-up exams conducted between 2002 and 2012. For this analysis, we used data from two studies ancillary to MESA: the MESA Stress Study and the MESA Air Pollution Study (MESA Air). The present study was limited to participants enrolled in the MESA Stress Study, which comprised MESA participants of white, black, and Hispanic race/ethnicities recruited from two of the six MESA sites, New York and Los Angeles, during the third and fourth follow-up exams for the parent study (2004–2006). Approximately 500 participants were enrolled in each site (total $N = 1,002$); 60% of visits were completed during the spring and fall, and 40% occurred during winter and summer. Our analysis also used data from the MESA Air Study (Kaufman et al. 2012), which conducted an extensive air pollution monitoring campaign in the six MESA sites to enhance existing federal monitoring data. Additional participant recruitment and measurement of subclinical measures of CVD conducted specifically for the MESA Air Study were not used in the present analysis.

Urinary Catecholamines

Urinary catecholamine data were obtained from participants enrolled in the MESA Stress Study. All three urinary catecholamines were assayed from 12-h pooled overnight urine. Participants were asked to collect all voids beginning 11 h before their anticipated wake-up time and ending one hour after waking up and to record the start and end time of urine collection. Samples were stored in the refrigerator if they were not brought back to the clinic shortly after last urine collection. Participants were also asked to record any missed or spilled specimens and to indicate any medications taken during the 24 h preceding their anticipated stop time. In clinical settings, 12-h overnight urine collection has been shown to correlate strongly with the gold standard 24-h collection (Fine et al. 2009; Stout et al. 2015). Importantly, 12-h urine collection improves compliance and reduces participant burden relative to 24-h collection, an important consideration for MESA Stress Study participants who collected their own urine samples.

Aliquots of urine were acidified to a pH ≤ 3 and frozen at $-80^{\circ}C$ until assayed. Samples were analyzed using high-performance liquid chromatography with electrochemical detection (Macdonald and Lake 1985). Intra- and interassay coefficients of variation were, respectively, 3.2% and 6.7% for EPI, 2.3% and 2.6% for NE, and 2.8% and 3.2% for DA. Catecholamine concentrations were adjusted for total urine volume and then divided by creatinine concentrations to account for differences in hydration (Djuric et al. 2008; Greenberg and Levine 1989).

Air Pollution

Long-term air pollution predictions were obtained from MESA Air as the annual average of the year prior to the date of urine collection for all MESA Stress Study participants. We examined several ambient pollutants, including $PM_{2.5}$, nitrogen dioxide (NO_2), oxides of nitrogen (NO_x), and black carbon (BC) as measured by light absorption coefficient. We also evaluated an additional measure of $PM_{2.5}$, which integrates infiltration into the home and time–location information; it can be considered an ambient-origin individual-level $PM_{2.5}$ metric and is referred to as "individual $PM_{2.5}$ in the text and tables (Allen et al. 2012; Spalt et al. 2015). Air pollution concentrations were predicted at the residential address of the participant and reflected all addresses at which the participant lived during the year prior to urine collection for those who moved within the MESA study area.

As has been described elsewhere, long-term concentrations of pollutants were calculated from a validated spatiotemporal prediction model (Kaufman et al. 2012; Keller et al. 2014). Briefly, this model, a city-specific land use regression model in a universal kriging framework, incorporated data from existing (i.e., the U.S. Environmental Protection Agency's Air Quality System) and study-specific air pollution monitors, geographic covariates such as distance to roads and land use characteristics, and outputs from dispersion models.

Associations with short-term $PM_{2.5}$ concentrations were considered a secondary analysis because the MESA Air Study was not optimized to evaluate short-term exposures. Short-term concentrations were calculated using one central site monitor in New York and three in Los Angeles, because these monitors recorded daily $PM_{2.5}$ levels (others had more erratic or inconsistent monitoring schedules) using the federal reference method. These concentrations reflect temporal rather than spatial variability in $PM_{2.5}$. Short-term metrics were not calculated for NO_2, NO_x, or BC. Given these pollutants' greater spatial variability, we were concerned that temporal contrasts could be highly inaccurate for participants living far from monitors. Furthermore, some daily central site monitors for these pollutants collected data only intermittently (e.g., once every 3 or 6 d), making it difficult to assess short-term temporal variation. Associations with short-term exposures were estimated based on the average daily exposure on the day of urine collection (lag0), the previous day (lag1), and for moving averages during the 2, 3, 4, and 5 d before urine collection (lag1–2, lag1–3, lag1–4, and lag1–5, respectively). Short-term $PM_{2.5}$ concentrations were adjusted for splines for calendar time [12 degrees of freedom (df)/year], temperature (6 df/year), relative humidity (6 df/year) and an indicator variable for day of the week prior to being regressed against the catecholamine data. Using a separate model to adjust for factors important to short-term $PM_{2.5}$ (preadjustment) has been shown to be an effective alternative to standard semiparametric adjustment and can increase precision in the final health effects estimates (Szpiro et al. 2014).

Covariates

Covariates included in these analyses were decided *a priori* after constructing a directed acyclic graph (Figure S1). Age, race/ethnicity (specified as white, black, or Hispanic from self-report), gender, study site, and both neighborhood and individual socioeconomic status (SES) were included in the models. A neighborhood disadvantage index (NDI) was derived from factor analysis of census tract–level data and specified so that higher values correspond to higher neighborhood SES (i.e., less deprivation) (Hajat et al. 2013). Data from the 2005–2009 American Community Survey were used to calculate NDI. Individual SES was defined as education ($\leq$high school, some college, or $\geq$college degree), income–wealth index (0–8 point scale, with higher values indicating more assets and income) (Hajat et al. 2010), and employment status (working outside the home vs. not). In addition, smoking status (current, former, or never smoker), secondhand smoke exposure (SHS) (yes or no, with no being 0 h per week in close contact with smokers, and yes otherwise), and current alcohol consumption (yes or no in response to a question about current alcohol consumption) were assessed via questionnaire. Measured height and weight were used to calculate body mass index (BMI, weight in kilograms divided by height in meters squared), which was specified as continuous in main effect models. Medication use (diuretics and/or sympathomimetic drugs such as adrenergic blockers) was ascertained from prescription and nonprescription drugs brought into clinic visits by participants. Emotional support, measured by the Enhancing Recovery in Coronary Heart Disease Patients Study Social Support Instrument, ranged from 6–30 points, where higher scores indicated more social support (Mitchell et al. 2003). Chronic burden was measured by a 5-point summary of stressful life events, with the number of points representing the number of stressful events (ranging between 0 and 5) (Bromberger and Matthews 1996). Race/ethnicity, gender, site, and education were time-invariant covariates, whereas all other covariates were measured when participants were seen for their MESA exam visit, usually a few weeks or months prior to their Stress Study visit.

Statistical Analysis

Participants were excluded from analysis for the following reasons: They collected less than 300 ml of urine ($n = 57$); they showed extreme catecholamine levels, i.e., NE > 140 ng/mg ($n = 4$), EPI > 26 ng/mg ($n = 4$) or DA > 800 ng/mg ($n = 5$); catecholamine values were below the level of detection (only for EPI, $n = 17$); or they were taking medication for Parkinson's Disease (only for DA analysis, $n = 3$). Extreme catecholamine values were excluded to reduce the skewness of the data. An additional three participants had missing catecholamine data. Between 45 and 92 participants were missing long-term air pollution predictions (depending on the pollutant), usually as a result of poor or missing residential address data. Also, short-term $PM_{2.5}$ predictions could not be made for seven participants because the date of urine collection was missing.

EPI, NE, and DA were log-transformed [ln (x)] in order to present results as percent differences and to improve normality of the data. Ordinary least squares regression with complete case analysis was used to analyze associations with both short- and long-term exposure (final sample sizes are shown in Supplemental Tables). A model staging approach was used where incrementally additional covariates were added to each subsequent model. Model 1 was adjusted for age, race/ethnicity, gender, and study site. Model 2 was adjusted for all the covariates in model 1 plus individual SES (education, employment, and income–wealth index) and NDI. Model 3 was adjusted for all the covariates in model 2 plus the CVD risk factors (smoking, secondhand smoke exposure, alcohol consumption, and BMI) as well as medication use, emotional support, and chronic burden. We considered model 3 to be the primary model of interest. Hypertension, diabetes, and other downstream health conditions may be acting as either colliders (i.e., they may be effects of both air pollution and catecholamines) or are in the causal pathway between air pollution and catecholamines (i.e., people with untreated hypertension have elevated catecholamine levels). Regardless of which role they play, adjustment for these factors in primary models would be inappropriate.

In addition, we conducted sensitivity analyses. In the short-term analyses, for a subset of participants, data on activities and stress levels on the day of urine collection were available. Sensitivity analysis adjusted for these acute stress covariates. We also evaluated sensitivity of results to using 6 or 8 df splines instead of 12 df splines in creating the adjusted short-term exposure measures to protect against overfitting of the models. We further adjusted short-term models for long-term ambient $PM_{2.5}$ concentrations and the other covariates specified in model 3. Finally, in the long-term analysis, we adjusted for season of urine collection (winter, spring, summer, and fall) because several related biomarkers have been shown to display seasonal trends (e.g., population-wide C-reactive protein levels are higher in the winter) (Halonen et al. 2010; Hampel et al. 2010).

Results

In Table 1, we present descriptive statistics for the sample ($n = 945$) after excluding participants with less than 300 ml of urine. Data for individual covariates were missing for ≤3% of participants. The study population was more than half Hispanic origin and over a quarter African American, about 9% were current smokers, the mean age was 65 y, and the mean BMI was 29 kg/m^2.

Boxplots of ambient $PM_{2.5}$, NO_x and NO_2 concentrations are provided in Figure 1. Given that only two of the six MESA sites were used in this study, the variability in pollutant levels is smaller than in other MESA studies; we observed that Los Angeles had higher $PM_{2.5}$ concentrations and that New York showed higher NO_x and NO_2 concentrations. Parameter estimates were reported for a 1 standard deviation (SD) unit increase in each of the pollutants: 2.1 $\mu g/m^3$ for ambient and individual

Table 1. Descriptive statistics [number (%) and mean (±standard deviation (SD)] for MESA stress study participants ($n = 945$), 2004–2006.

Participant characteristic	n (%) or mean ± SD
Demographics & cardiovascular disease risk factors	
Age (years)	65 ± 9.7
Female (%)	497 (52.6)
Male (%)	448 (47.4)
Black (%)	264 (27.9)
Hispanic (%)	504 (53.3)
White (%)	177 (18.7)
New York (%)	486 (51.4)
Los Angeles (%)	459 (48.6)
≤High school degree (%)	452 (47.8)
Some college (%)	282 (29.8)
≥College degree	211 (22.3)
Working outside the home (%)	479 (50.7)
Not working outside the home (%)	466 (49.3)
Income-wealth index[a]	3.8 ± 2.3
Missing (n)	3
Neighborhood disadvantage index[b]	−0.3 ± 1.5
Missing (n)	29
Body Mass Index (kg/m^2)	29 ± 5.6
Missing (n)	1
Current smokers (%)	83 (8.8)
Former smokers (%)	435 (46.3)
Never smokers (%)	422 (44.9)
Missing (n)	5
Exposed to secondhand smoke (%)[c]	291 (31.1)
Not exposed to secondhand smoke (%)	645 (68.9)
Missing (n)	9
Current alcohol use (%)	407 (43.1)
No current alcohol use (%)	537 (56.9)
Missing (n)	1
Medication use (%)[d]	192 (20.7)
No medication use	735 (79.3)
Missing (n)	18
Psychosocial stress	
Chronic Burden[e]	1.2 ± 1.3
Missing (n)	5
Emotional support[f]	27.0 ± 6.0
Missing (n)	6

[a]Measured on 9-point scale, where 0 is the fewest assets and lowest income, and 8 is highest.
[b]Derived from factor analysis of 21 census variables at the census tract level; higher scores indicate higher neighborhood SES.
[c]Smokers are included as exposed to secondhand smoke.
[d]Medication use includes use of diuretics and/or sympathomimetic drugs such as adrenergic blockers.
[e]Chronic burden measured on scale between 0 and 5; higher scores indicate more chronic burden.
[f]Emotional support measured on scale from 6 to 30, where higher scores indicate more emotional support.

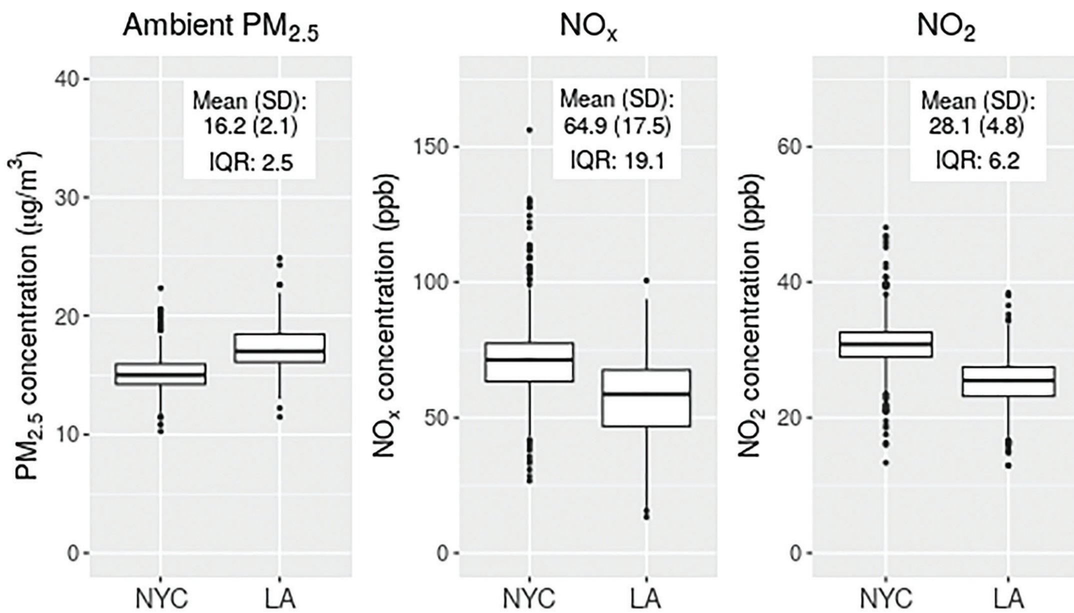

Figure 1. Boxplots of ambient $PM_{2.5}$ and NO_x by study site. The black line in the middle of the box indicates the median; the top edge of the box indicates the upper quartile (75%); the bottom edge of the box indicates the lower quartile (25%); the whiskers (lines extending from the boxplot) represent 1.5 times the interquartile range. The highest point indicates the maximum value and the lowest the minimum value.

$PM_{2.5}$, 17.5 ppb for NO_x, 4.8 ppb for NO_2 and 0.2 10^{-5}/m for black carbon. SD were similar to interquartile ranges: 2.5 $\mu g/m^3$ for ambient $PM_{2.5}$, 2.7 $\mu g/m^3$ for individual $PM_{2.5}$, 19.6 ppb for NO_x, 6.2 ppb for NO_2 and 0.2 10^{-5}/m for black carbon. All three catecholamines had a skewed distribution, which was most pronounced for EPI (Figure 2). After log transformation (histograms not shown), distributions of the catecholamines were normally distributed.

Fully adjusted estimates (Model 3) for associations with NE were positive for a 2.1 $\mu g/m^3$ (1-SD) increase in long-term ambient $PM_{2.5}$ (2.5%; 95% CI: −1.2, 6.3) and a 17.5 ppb increase in long-term NO_x (3.5%; 95% CI: −0.4%, 7.6%) (Figure 3). The associations between NE and the other pollutants were null.

EPI was positively associated with 1-SD increases in long-term ambient $PM_{2.5}$ (9.1% higher; 95% CI: 3.2, 15.3%), individual $PM_{2.5}$ (6.3%; 95% CI: 0.6, 12.2%), NO_x (6.3%; 95% CI: 0.3, 12.6%), and NO_2 (5.2%; 95% CI: −1.0, 11.7% for a 4.8-ppb increase) based on fully adjusted models (Figure 3).

DA was also positively associated with 1-SD increases in long-term $PM_{2.5}$ (4.4% higher; 95% CI: 1.0, 7.9% and 3.5% higher; 95% CI: 0.1, 7.0% for ambient and individual exposures, respectively). We found a weak but positive association between DA and NO_x (1.5% higher; 95% CI: −2.0, 5.2%), whereas associations were null for NO_2 and BC. In general, fully adjusted (Model 3) estimates were closer to the null than were estimates from Models 1 and 2 for most exposures and outcomes (Table S1).

The associations between short-term $PM_{2.5}$ and the catecholamines were largely null. Associations of air pollution on the day of urine collection (lag 0) were weak but positive for EPI and DA and null for NE; associations were weak and inverse for the rest of the lag periods and outcomes (Table 2 and S2).

Sensitivity analyses did not produce substantively different results. First, in models adjusted for activities and stress levels on the day of urine collection, we saw little change in point estimates for the short-term analysis (Table S3). Second, in the

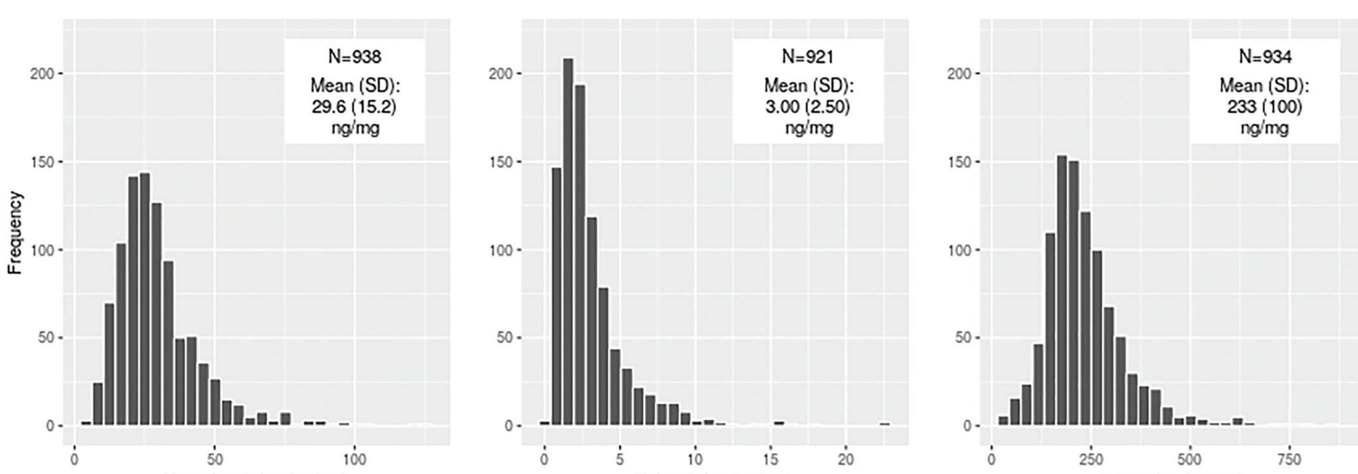

Figure 2. Histograms of NE, EPI and DA concentrations from 12-h urine samples prior to log transformation.

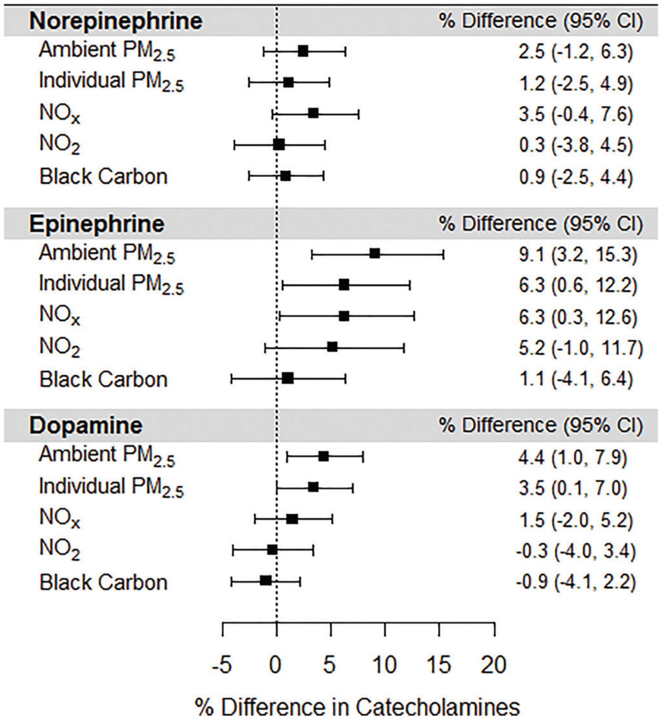

Figure 3. Percent differences and 95% confidence intervals in stress hormones per 1 standard deviation (SD) unit higher long-term pollutant concentrations. SD increases are as follows: $2.1\ \mu g/m^3$ for ambient and individual $PM_{2.5}$, 17.5 ppb for NO_x, 4.8 ppb for NO_2 and $0.2\ 10^{-5}/m$ for black carbon(BC). Models were adjusted for age, race/ethnicity, gender, site, education, employment status, income–wealth index, neighborhood disadvantage index, smoking, secondhand smoke exposure, BMI, alcohol consumption, emotional support, chronic burden, and medication use. The number of observations and estimates corresponding to Models 1 and 2 are reported in Table S1.

short-term preadjusted estimates, a sensitivity analysis using 6 df and 8 df instead of 12 df splines for calendar time showed little difference in parameter estimates across models. Specifically, the NE and DA results changed very little across models, whereas the EPI results were attenuated or augmented by three tenths of a percent at most (Table S4). Thus, we do not believe the models with 12 df were overfitted. Third, short-term models were adjusted for long-term ambient $PM_{2.5}$ concentrations and the other covariates specified in model 3. In general, associations with short-term exposures were closer to the null after additional adjustment for long-term ambient $PM_{2.5}$, but there was little change in the width of their 95% CI (Table S5). Last, in the long-term analysis we adjusted for season of urine collection as a covariate and observed little change in the parameter estimates (Table S6).

Table 2. Percent differences (95% confidence intervals) in stress hormones per 1 standard deviation (SD) $\mu g/m^3$ higher short-term $PM_{2.5}$ concentrations.

Short-term $PM_{2.5}$ concentration	NE	EPI	DA
lag0	−0.2 (−3.3, 3)	1.1 (−3.7, 6)	1.1 (−1.8, 4.1)
lag1	−2.1 (−5.4, 1.1)	−2.2 (−7.2, 2.5)	−2.2 (−5.2, 0.8)
lag1–2	−1.5 (−4.8, 1.8)	−2.5 (−7.5, 2.3)	−2.5 (−5.6, 0.4)
lag1–3	−1.9 (−5.2, 1.4)	−2.9 (−7.9, 2)	−2.2 (−5.2, 0.8)
lag1–4	−2.5 (−5.9, 0.7)	−3.8 (−8.9, 1.1)	−2.7 (−5.8, 0.3)
lag1–5	−2.1 (−5.4, 1.2)	−3.0 (−8.1, 1.9)	−2.1 (−5.1, 0.9)

Note: Standard deviation (SD) increases are as follows: day of urine collection 8.3, day prior 7.9, 2-day average 7.1, 3-day average 6.5, 4-day average 6.0, and 5-day average $5.6\ \mu g/m^3$. Short term concentrations were preadjusted using splines for calendar time, temperature, relative humidity, and an indicator variable for day of the week. Models adjusted for age, race/ethnicity, gender, site, education, employment status, income-wealth index, neighborhood disadvantage index, smoking, secondhand smoke exposure, BMI, alcohol consumption, emotional support, chronic burden, and medication use (model 3). Estimates for models 1 and 2 are reported in Table S2.

Discussion

Higher long-term $PM_{2.5}$ exposures were associated with higher urine EPI and DA concentrations in MESA Stress Study participants, an ethnically diverse population of adult residents of urban New York and Los Angeles in 2004–2006. In addition, long-term NO_x exposures were associated with higher EPI concentrations. Long-term air pollution exposures were not significantly associated with urine NE concentrations, and findings did not support associations between any of the outcomes and $PM_{2.5}$ concentrations on the same day or up to 5 d prior to urine collection.

Detailed mechanisms have been proposed to explain acute effects of air pollution on stress hormones in experimental settings (Kodavanti 2016; Snow et al. 2018), but less information exists regarding potential mechanisms for effects of long-term exposures on these outcomes. One hypothesized mechanism by which air pollution causes systemic health effects is through induction of the inflammatory pathway whereby pollution-induced pulmonary inflammation spills over into circulation, driving systemic effects (Brook et al. 2010). Recent work suggests that stress hormone receptors, specifically beta-adrenergic receptors, play an important role in the inflammatory process and that alterations of these receptors may induce long-term health effects. By blocking these receptors (through pharmacological intervention), researchers observed a reduction in inflammatory cytokines and neutrophilic inflammation in the lung following exposure to ozone (Henriquez et al. 2018); similarly, agonists of these receptors have been shown to increase inflammatory cytokines released following exposure to PM *in vitro* (Chiarella et al. 2014). Adrenergic receptors are expressed on a variety of immune and inflammatory cells, thus allowing these receptors to play a role in coordinating the systemic inflammatory response (Flierl et al. 2008). In fact, researchers have shown that immune and inflammatory cells synthesize, store, and release catecholamines (Flierl et al. 2008; Kempuraj et al. 2017). The direct role of EPI (primarily produced by the adrenal gland) in the inflammatory process has been suggested in a study in which removal of the adrenal gland in rats resulted in a reduction of ozone induced lung damage and pulmonary inflammation (Miller et al. 2016). Although the specific mechanisms that could link long-term air pollution exposure to catecholamine levels have yet to be identified, the complex relations between exposure, inflammatory responses, and stress biology implied by prior work suggest that such an effect is biologically plausible.

Furthermore, the potential translocation of PM and its constituents into the systemic circulation, another hypothesized mechanism (Brook et al. 2010), may also play an important role in activating the SNS. This mechanism may involve the alteration of stress hormone receptors, which are found in all organ systems. Given the role of these receptors in regulating important processes throughout the body (e.g., nutritional supply to cells and immune surveillance), any alteration in function could result in health impacts over time. The presence of receptors throughout the body may also explain how inhaled PM and other pollutants can produce a broad range of health effects, whether directly (translocation) or indirectly (inflammation). Direct mechanisms for effects of air pollutants on catecholamine release have also been proposed. For example, inhaled pollutants might trigger lung receptors that, through autonomic afferents, produce a net sympathetic response leading to an increase in circulating catecholamines (Kodavanti 2016; Snow et al. 2018).

We hypothesize that long-term exposure to air pollution is associated with chronic release of catecholamines, which could lead to desensitization or down-regulation of catecholamine receptors (Hausdorff et al. 1990). Prolonged elevation of catecholamine levels is thought to contribute to the development of atherosclerosis and to predispose people to hypertension, myocardial ischemia, and arrhythmias. Elevated catecholamine levels make blood more prone to coagulation, increasing the risk of arterial obstruction and myocardial infarction (Mustonen and Lassila 1996; Preckel and von Känel 2004). Thus, chronic effects of long-term exposure to air pollution on catecholamine levels might contribute to CVD and may be relevant to recently reported association between air pollution and neurodegenerative outcomes (Kioumourtzoglou et al. 2016; Ritz et al. 2016).

Findings from experimental studies provide some support for an association between long-term $PM_{2.5}$ exposure and DA. A controlled human exposure study reported that in 13 adult volunteers (8 with and 5 without metabolic syndrome), the increase in plasma L-DOPA (a precursor to DA) after a 2-h exposure to diesel exhaust was significantly greater than the corresponding increase after the same exposure to filtered air (Peretz et al. 2008). In contrast, the increase in plasma NE after exposure to diesel exhaust was not significantly different from the increase after exposure to filtered air. One day after adult rats were exposed to concentrated $PM_{2.5}$ for 8 h, DA was significantly higher in one brain region in comparison with levels in the same region among rats exposed to filtered air, whereas DA levels were lower in another region, though not significantly so (Sirivelu et al. 2006). In another study, 12-wk-old male offspring of rats exposed to diesel exhaust particles on gestational days 1–17 had significantly higher tissue concentrations of DA in two of four brain regions following a resident–intruder test than the male offspring of dams exposed to filtered air had (Yokota et al. 2016). Other studies, however, have reported that tissue concentrations of DA and its metabolites in some brain regions were lower in exposed animals in comparison with control animals (Allen et al. 2017). DA concentrations were measured in urine samples from MESA Stress Study participants, which may or may not reflect circulating levels or tissue-specific concentrations in the brain. In addition, exposures used in experimental studies are often substantially higher than ambient concentrations.

We observed a positive but nonsignificant association between NE and NOx and NE and ambient $PM_{2.5}$. Several animal studies have reported increases in NE with exposure to PM. Researchers have reported increases in urinary NE after a 6-month exposure to $PM_{2.5}$ in mice (Ying et al. 2014), higher NE concentration in the paraventricular nucleus of the rat brain after 8 h of exposure to PM (Sirivelu et al. 2006), increases in hypothalamic NE after one- to three-day exposure to $PM_{2.5}$ in rats (Balasubramanian et al. 2013), and increases in NE in mouse tissue after exposure to PM for 8 h/d for 3 d (Chiarella et al. 2014).

Furthermore, a recent randomized crossover study of 55 nonsmoking college students in Shanghai, China, reported that serum NE and EPI concentrations were 1.57 and 1.2 times higher, respectively, following 9 d of sham purifier use relative to concentrations after 9 d of dormitory air purification with a high-efficiency air purifier (Li et al. 2017). In a controlled exposure study, 50 nonsmokers age 18–40 y had nonsignificant increases in urine concentrations of vanillymandelic acid (VMA), a major urinary metabolite of NE and EPI, 1 h after exposure to coarse and ultrafine concentrated ambient particles in comparison with concentrations after exposure to filtered air and significantly higher urine VMA 21 h after coarse particle exposure. In contrast, no consistent differences in urine concentrations of homovanillic acid, a major urine DA metabolite, were found after exposure to concentrated particles (Liu et al. 2017). To our knowledge, the only other published study on air pollution and EPI was a cross-sectional study of 597 9- to 11-y-old Polish children from an industrial region that used bivariate analysis stratified by gender to estimate associations between exposure to NO_x and urinary catecholamines measured using a spectrofluorimetric assay (Orgacka et al. 1983). Towns in the study region were divided into groups of high-, medium-, and low-NO_x concentrations; towns with the lowest concentrations served as a control group. NOx concentrations were based on measurement from 2–4 monitoring sites in the region. The authors reported significantly higher mean urine DA and NE concentrations in girls from towns with low levels of NO_x in comparison with those living in control towns but no significant differences in urinary EPI. To our knowledge, studies by Orgacka et al. (1983) and Li et al. (2017) were the only two human studies that examined the association between EPI and air pollution.

Although NE had weak positive associations with ambient $PM_{2.5}$ and NO_x only, EPI had relatively strong associations with all long-term exposures except exposures to BC. Differences between the two outcomes may reflect functional and physiological differences between the catecholamines. For example, EPI is primarily made and released in the adrenal gland, whereas almost 80% of NE is locally released and interacts with adrenergic receptors in target tissues (Kodavanti 2016). Effects of air pollution on tissue-level NE concentrations, if present, might not produce detectable changes in urinary NE concentrations.

In terms of other findings, the stronger associations seen for long-term ambient $PM_{2.5}$ in comparison with individual $PM_{2.5}$ were expected. Individual long-term $PM_{2.5}$ exposure accounted for infiltration of ambient air into participant residences and time spent indoors and thus was expected to reduce Berkson error and thereby increase the precision of effect estimates relative to those for ambient $PM_{2.5}$ concentrations (Szpiro and Paciorek 2013). However, limitations of the data used to estimate air infiltration, (e.g., error related to questionnaire data on window opening frequency during typical summer and winter months, use of air filters, and frequency of air conditioning use) (Allen et al. 2012) may have increased classical measurement error, which would bias effect estimates toward the null (on average) and thus may at least partly explain weaker associations with estimates of individual vs. ambient long-term $PM_{2.5}$ exposure.

We found that NO_x had a stronger association with NE and EPI than did NO_2. This finding implies that a measure of NO (a marker of fresh mobile source emissions that was not available for this analysis) could be an even stronger predictor. In addition, long-term BC exposure estimates were likely to have greater classical measurement error in comparison with other pollutants, which may have biased associations and led to null findings.

Although the null findings in the short-term air pollution analysis were unexpected, we believe there are several possible reasons for these results. First, short-term exposure estimates were based on central site monitoring and are purely temporal; i.e., they do not account for the spatial distribution of $PM_{2.5}$. The null associations seen in the short-term air pollution analysis may be a result of spatial measurement error in the exposure. Measurement error in environmental epidemiology studies is arguably one of the most significant threats to inference. In addition, some residual confounding of the short-term exposures may exist, in that we may not be fully capturing the temporal covariates related to both $PM_{2.5}$ and catecholamines through adjustment for temperature, relative humidity, and calendar time splines. Second, short-term catecholamine effects may operate on an hourly not daily scale, so our exposure periods are too long. We would need both catecholamines and air pollution to be measured at hourly time intervals in order to capture these shorter-term effects. The timing of urine collection noted above may have also influenced our short-term results in that fewer participants had urine collection during months when air pollution concentrations are generally higher (Peng et al. 2005).

The magnitudes of effect in our study were relatively small. We observed about a 9% higher EPI and 4.4% higher DA level associated with a 2.1 $\mu g/m^3$ (1-SD) higher long-term ambient $PM_{2.5}$. For comparison, EPI levels have been estimated to increase about two to three times that of resting levels during a mild stressor, such as a public speaking task, and eight to ten times that during a more severe stressor, such as childbirth (Alehagen et al. 2005; Kudielka et al. 2007). Although these increases are seen in times of more acute stress, it is reasonable to expect that much smaller increases, when extended over long periods of time (such as those resulting from chronic environmental exposures such as air pollution), could have important health consequences.

There are several limitations to our study. First, given the largely cross-sectional nature of this study, we could not evaluate temporal relations between the exposures and outcomes. Given considerable variability in catecholamine levels, having repeat measures over time may provide a more robust inference. Second, our results may be biased due to residual or unmeasured confounding. Residual confounding from neighborhood SES or unmeasured confounders such as noise may bias effect estimates. In addition, many of the psychosocial stress covariates in the short-term analysis are measuring chronic not acute stressors. We did, however, conduct sensitivity analysis with some available data on acute stressors and found little difference in effect estimates (Table S3). Third, research has not yet established which exposure time windows are relevant to the relationship between long-term cumulative air pollution and stress hormone dysregulation. Exposures over longer time periods (e.g., during the previous five or ten years) would have been underestimated by the annual average concentrations used in our analysis given the decline in air pollution over time. Last, findings based on elderly MESA participants of white, black, and Hispanic races/ethnicities from the urban New York and Los Angeles study sites may not be generalizable to other populations, and additional studies are needed to determine whether results extend to other age groups and locations and to assess the potential influence of chance or bias.

The strengths of our study include high-quality exposure assessment, outcome ascertainment, and a diverse population. The strengths of our exposure-assessment approach have been well documented (Kaufman et al. 2012). Catecholamine concentrations in 12-h urine samples should provide a better measure of usual catecholamine levels than do concentrations in single spot urine samples, which is an advantage for studying long-term effects of air pollution on catecholamines. Last, we currently have a paper under review that examines the association between air pollution and cortisol in the MESA population. This work will add to our knowledge of how air pollution affects the body's stress response systems.

Additional mechanistic and *in vivo* experimental research is needed to clarify mechanisms underlying the chronic health effects of long-term air pollution exposures, including potential effects and outcomes related to activation of the SNS, and to identify biological processes that might be targeted to reduce or prevent such effects. Furthermore, observational studies of other populations and of exposures and outcomes measured over different time periods are also needed to support and clarify our findings.

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